REMARKS

I. Status of the Claims

Claims 1-42 are pending and under consideration.

II. Rejections Under 35 U.S.C. §§ 102(b) and 103(a)

According to the Office, claims 1, 4-8, 11-26, 34 and 35 are anticipated by, and claims 2, 3, 9, 10, 27-33 and 36-42 are obvious over, File *et al.*, J. Chemotherapy, Vol. 12, pages 314-25 (August 2000) ("File"). Office Action, page 2 and 3.

Applicant respectfully traverses. The Office asserts that File is available as a reference under 35 U.S.C. § 102(b). *Id.* at 2. M.P.E.P. § 2128 reviews the criteria for determining the date on which a publication becomes available as a reference. A journal article is not available as prior art *until* it is received by a member of the public. M.P.E.P. § 2128.02 (citing *In re Schlittler*, 234 F.2d 882, 110 U.S.P.Q. 304 (CCPA 1956). As shown in the attached Exhibit, the library at the National Institutes of Health did not receive the Journal of Chemotherapy, volume 12, no. 4 until November 3, 2000. The date stamp for that journal appears on the first page of the first article in that volume, which is entitled "Multiantibiotic Resistance of Gram-Negative Bacteria Isolated from Drinking Water Samples in Southwest Greece." The date stamp thus provides evidence that the File reference was first available to the public on November 3, 2000.

This application claims benefit of provisional application no. 60/232,809, filed September 15, 2000, and provisional application no. 60/245,744, filed November 3, 2000. Consequently, File is not available as a reference under 35 U.S.C. § 102(b), nor is it a reference under 35 U.S.C. § 102(a) because that section requires that the

reference describe the invention in a printed publication "*before* the invention thereof by the applicant for patent in the United States." 35 U.S.C. § 102(a) (emphasis added).

File is not available as a reference under any section of 35 U.S.C. § 102. Accordingly, Applicant respectfully requests withdrawal of the rejections of record under 35 U.S.C. § 102(b) and 35 U.S.C. § 103(a) based upon the File reference.

Conclusion

In view of the foregoing remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: December 8, 2005

By: _____

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Multiantibiotic Resistance of Gram-Negative Bacteria Isolated from Drinking Water Samples in Southwest Greece

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Summary

In this study we monitored the sensitivity of 239 Gram-negative bacteria (of fecal and non-fecal origin), isolated from the old drinking water distribution network of Patras in southwestern Greece, to 20 antibiotic agents. Two methods were used to find the multiresistant bacteria (bacteria resistant to two or more antibiotics): the diffusion disk method and a serial dilution method. The Gram-negative bacteria tested were: *Enterobacteriaceae* (62), *Pseudomonas* (145), *Vibrionaceae* (24), *Chromobacter* (3), *Acinetobacter* (2) and others (4). The highest levels of antibiotic resistance were obtained for cephalothin (86.7%), ampicillin (77.5%) and carbenicillin (71%) followed by cefoxitin (55.4%) and cefuroxime (51.2%). Intermediate resistance levels were found for ticarcillin (31.3%), ceftizoxime (31.2%), chloramphenicol (30.3%), and cefotetan (25.2%). Low resistance levels were obtained for cefotaxime (17.9%), sulfisoxazole (15.2%), ceftriaxone (12.5%), tetracycline (11.9%), trimethoprim/sulfamethoxazole (7.4%) and piperacillin (2.4%). Overall 91.3% of the Gram-negative bacteria isolated from drinking water were multiresistant. No resistant strains were found to quinolones, aminoglycosides, imipenem, aztreonam, ceftazidime or cefoperazone. The high antibiotic resistance rate of the isolated microorganisms from the Patras drinking water supply is discussed.

Key words: **Antibiotic resistance, multiresistant bacteria, drinking water, Greece.**

INTRODUCTION

The occurrence of multiantibiotic resistant bacteria in the potable water of all municipal distribution systems has significantly increased [1,2,3,4,5]. The increase in bacterial pathogens observed in municipal water systems has been demonstrated in many studies and is significant

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Gemifloxacin versus Amoxicillin/Clavulanate in the Treatment of Acute Exacerbations of Chronic Bronchitis

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Summary

Six hundred patients were evaluated in this randomized, double-blind, double-dummy, multicenter, parallel-group study comparing the efficacy and safety of gemifloxacin (320 mg once-daily for 5 days) and amoxicillin/clavulanate (500/125 mg three-times daily for 7 days) for the treatment of acute exacerbations of chronic bronchitis (AECB). Of note, more than 90% of study participants had stage 2 disease at study entry. The two drugs were found to be equally effective, with clinical success rates of 93.6% for gemifloxacin and 93.2% on amoxicillin/clavulanate (95% CI -3.9 to 4.6). Bacteriological success rates favored gemifloxacin (90.9% compared with 79.5% for amoxicillin/clavulanate; 95% CI -3.3 to 26.0); however, this difference was not statistically significant. Gemifloxacin and amoxicillin/clavulanate were both well tolerated. In summary, gemifloxacin was found to be well tolerated and effective for the treatment of AECB, suggesting it is well suited for empirical treatment of this common respiratory condition in the current clinical environment.

Key words: **Gemifloxacin, amoxicillin/clavulanate, chronic bronchitis, efficacy, safety, clinical trial, fluoroquinolone, quinolone.**

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INTRODUCTION

Chronic bronchitis is frequently encountered in routine clinical practice, affecting as many as 15-21% of the adult population in the USA alone [1]. Chronic bronchial disease predisposes patients to frequent lower respiratory tract infection, with acute exacerbations of chronic bronchitis (AECB) accounting for approximately 12 million physician visits and 10% of hospital admissions annually [2,3]. Bacterial infection accounts for the majority of all AECB episodes, with *Haemophilus influenzae, Streptococcus pneumoniae* and *Moraxella catarrhalis* being the predominant causative organisms in 85-95% of cases [4]. The most usual treatment approach is consequently empirical antibiotic therapy directed at these three pathogens.

Choice of appropriate antibacterial therapy for AECB is becoming more difficult, however, due to the increasing prevalence of antibiotic resistance in the principal causative pathogens. In the USA, for example, almost all clinical isolates of *M. catarrhalis* (>95%) and some 38% of *H. influenzae* isolates produce β-lactamases [5,6]. This results in resistance to some β-lactam antibiotics, most notably penicillin, and current estimates indicate a similar incidence of penicillin-resistance in *S. pneumoniae* (34%) [6]. The potential for cross-resistance between classes of antibacterial agents is a further concern, with available data demonstrating that many penicillin-resistant strains of *S. pneumoniae* will not be susceptible to oral cephalosporins and macrolides [6,7]. Although most data on antibiotic resistance are currently derived from North America, similar trends have been observed in Europe [8,9].

One approach to overcoming this problem has been to combine amoxicillin with a β-lactamase inhibitor such as clavulanic acid. Clavulanate-potentiated amoxicillin has proven clinical efficacy in the treatment of AECB [10-12], and has recently been shown to be one of the most cost-effective antibacterials currently available for the clinical management of this condition [13]. Experience gained over the past 18 years has established that amoxicillin/clavulanate has an excellent safety profile and minimal interaction potential. As a result, it has become the 'gold standard' against which newer antibacterials are judged [14].

Fluoroquinolones have also been shown to be effective for the treatment of AECB [11,15-19], although the efficacy of older drugs of this class, such as ciprofloxacin, may be limited by their low intrinsic activity against clinically important Gram-positive species, most notably *S. pneumoniae* [20]. Newer fluoroquinolones, such as trovafloxacin, have a much broader spectrum of antibacterial activity. However, the potential for serious adverse effects with trovafloxacin has limited its clinical utility [21,22].

Gemifloxacin is a novel, broad-spectrum fluoroquinolone, which appears to be well suited for the treatment of AECB, having potent *in vitro* activity against *H. influenzae* and *M. catarrhalis* as well as *S. pneumoniae* [23-25]. Importantly, gemifloxacin retains this potent antibacterial activity against β-lactam and macrolide-resistant strains [23,24], and is also active against isolates of *S. pneumoniae* and *H. influenzae* with decreased susceptibility to ciprofloxacin [26,27].

The aim of this study was to compare the clinical and bacteriological efficacy and tolerability of gemifloxacin in the treatment of AECB with that of amoxicillin/clavulanate. Both antibacterials were administered orally, with dosing regimens of 320 mg once-daily for 5 days and 500/125 mg three-times daily for 7 days, respectively.

PATIENTS AND METHODS

Patients

Male or female patients (age ≥40 years), with a history of chronic bronchitis characterized by cough and sputum production for more than 2 consecutive years and for most days in a period of 3 consecutive months, were considered for enrollment into this trial. All patients were required to have an acute exacerbation (defined as increased purulent sputum, cough and dyspnea) suitable for treatment with an oral antibacterial to be eligible for study participation.

Exclusion criteria included: serious underlying respiratory disease (such as pneumonia, cystic fibrosis, tuberculosis, bronchiectasis or active pulmonary malignancies); a history of epilepsy, convulsions or myasthenia gravis; a history of hemolytic crisis or known glucose-6-

phosphate dehydrogenase (G6PD) deficiency; and presence of any other complicating infection, disease or condition that might compromise evaluation of the study drugs (such as HIV infection, renal impairment, abnormal liver function tests, alcohol or drug abuse). Patients with known or suspected hypersensitivity to quinolone, penicillins or other β-lactam antibacterial agents, or a history of tendonitis while taking fluoroquinolones were also excluded, as were pregnant or nursing women. Patients must not have received another antibacterial agent within 7 days of study entry, been treated with an investigational drug, vaccine or device within the past month or participated in a previous study of gemifloxacin. Concurrent use of sucralfate, probecenid or systemic steroids (>10 mg/day prednisolone or equivalent) was prohibited.

Study design

This was a double-blind, double-dummy, multicenter, parallel-group study. Patients were randomized to receive either: oral gemifloxacin (Factive®; SmithKline Beecham Pharmaceuticals, Harlow, UK) 320 mg once-daily for 5 days with oral amoxicillin/ clavulanate-placebo three-times daily for 7 days; or, oral amoxicillin/clavulanate 500/125 mg (Augmentin®; SmithKline Beecham Pharmaceuticals, Harlow, UK) three-times daily for 7 days with oral gemifloxacin-placebo once-daily for 5 days.

Patients were assessed at five clinic visits over a period of approximately 5 weeks: screening (Day 0), on-therapy (Day 2-4), end of therapy (Day 9-11), follow-up (Day 14-21) and long-term follow-up (Day 28-35). Full medical history was recorded at screening, and a physical examination conducted. A chest X-ray film was obtained at this visit, or within 48 h of enrollment, to preclude a diagnosis of pneumonia. Patients were also required to have had forced expiratory volume in one second (FEV_1) measured within the previous 12 months. If not, an assessment was scheduled for between the end of therapy and long-term follow-up. Vital signs, clinical signs and symptoms of AECB were evaluated at all visits, and auscultatory assessments were made for wheeze, rales and crepitations. Peak expiratory flow (PEF) was evaluated at screening, follow-up and long-term follow-up.

Sputum samples were collected at screening and, where possible, at the end of therapy, follow-up and long-term follow-up, or at the time of study withdrawal. Sputum was assessed in a central laboratory by Gram-staining, routine microbiology culture, and susceptibility testing (performed according to National Committee for Clinical Laboratory Standards guidelines [28]). Purulence, assessed by microscopy, was defined as ≥25 white blood cells per field and ≤10 squamous epithelial cells at 100x magnification; a sputum sample was only considered evaluable if these criteria were met. Only organisms identified from evaluable samples were regarded as pathogenic.

The study was conducted in accordance with Good Clinical Practice guidelines and the revised Declaration of Helsinki (1996). An institutional review board (or ethics committee) approved the protocol at each center, and all patients provided written informed consent.

Efficacy assessments

The primary efficacy measure was clinical response at follow-up. Secondary efficacy measures included clinical response at end of therapy and at long-term follow-up, and bacteriological response at end of therapy, follow-up and long-term follow-up.

Clinical outcome was determined by comparing signs and symptoms of AECB (severity of cough and dyspnea, auscultatory findings, evaluation of sputum characteristics) with those from the previous visit. At the end of therapy, clinical outcome was classed as *clinical success* (sufficient improvement/resolution of signs and symptoms such that no additional antibacterial therapy was indicated), *clinical failure* (insufficient improvement/deterioration of signs and symptoms such that additional antibacterial therapy was indicated) or *unable to determine* (an assessment could not be made). Patients designated a clinical success at end of therapy were assessed at follow-up, and outcome was determined as *clinical success, clinical recurrence* (reappearance or deterioration of signs and symptoms such that additional antibacterial therapy was indicated) or *unable to determine*. Patients who were clinical successes at follow-up were assessed at long-term follow-up and outcome determined as *clinical success, clinical recurrence* or *unable to determine*.

Bacteriological outcome based on sputum culture and Gram-staining was assessed for each patient at the end of therapy and at both follow-up visits and classified as: *eradication* (elimination/continued absence of initial pathogen from a repeat sputum culture); *presumed eradication* (absence of an evaluable repeat sputum culture in a patient who was a clinical success); *bacterial persistence/recurrence* (presence of original pathogen on repeat culture at the end of therapy/initial pathogen eradicated, or presumed eradicated at previous visit but reappeared); *presumed bacterial persistence/recurrence* (absence of evaluable repeat culture in a patient who was a clinical failure/clinical recurrence); *unable to determine*. A new pathogen isolated from a symptomatic patient who required additional antibacterial therapy was considered a *superinfection* at the end of therapy and a *new infection* at follow-up or long-term follow-up. New pathogens identified in non-symptomatic patients not requiring additional antibacterial therapy were categorized as *colonization*.

The per-patient bacteriological response (only applicable to patients with at least one initial pathogen) was defined as a *success* if all initial pathogens were eradicated or presumed eradicated, with no evidence of superinfection or any new infections. Bacteriological *failure* was defined as persistence (documented or presumed) of one or more initial pathogens or superinfection at the end of therapy visit, and as recurrence of one or more initial pathogens or a new infection at either of the follow-up visits. An assessment of *unable to determine* was also considered as *bacteriological failure*.

Safety assessments

Adverse experiences were elicited by non-leading questioning at each visit. All adverse events were recorded by WHO body system and preferred term, and classified by severity (mild, moderate or severe) as well as presumed relationship to the study drug (not related, unlikely, suspected or probable). Patients reporting adverse experiences were followed up until the condition had subsided or stabilized. Laboratory tests for hematology, clinical chemistry and urinalysis were performed at screening, on-therapy and at the end of therapy.

Statistical analysis

Assuming an underlying equivalent clinical response rate of 88% at follow-up, 444 patients (222 in each treatment group) were required to give a power of 90% to detect that the lower limit of the two-sided 95% confidence interval (CI) for a difference in rates (gemifloxacin minus amoxicillin/clavulanate) was no less than -10% (indicating non-inferior efficacy of gemifloxacin) [29].

Efficacy analyses were performed on four different data-sets: the intent-to-treat (ITT) population, comprising all randomized patients who took at least one dose of study medication; the bacteriology ITT population, consisting of ITT patients who also had at least one pathogen identified at screening; the clinical per-protocol (PP) population, comprising all ITT patients who adhered to the study protocol; and the bacteriology PP population, which included all bacteriology ITT patients who did not violate the protocol. Patients with an outcome of unable to determine were excluded from the PP populations. Safety analyses were performed using the ITT population.

All efficacy variables were analyzed by unstratified comparison of proportions between treatment groups for the clinical PP population. Two-sided 95% CIs were used to estimate the difference in proportion of successes between treatments. The analysis was repeated for the ITT population and similar analyses were carried out for the secondary efficacy variables. All other intergroup differences were evaluated using Fisher's exact test.

RESULTS

Patients' characteristics

A total of 600 patients were enrolled into this study, of whom 304 were randomized to treatment with gemifloxacin and 296 to amoxicillin/clavulanate. All patients received at least one dose of study medication and were therefore included in the ITT population. A total of 287 and 275 patients from the two groups, respectively, completed the study. Reasons for the 38 withdrawals included adverse experiences (10 and 9 patients, respectively), protocol deviations (6 patients in each group), insufficient therapeutic effect (further antibacterial

treatment indicated; 1 patient in each group), lost to follow-up (4 patients treated with amoxicillin/clavulanate) and patient request (1 patient in the amoxicillin/clavulanate group).

The clinical PP population at follow-up comprised 268 patients who had received gemifloxacin and 266 treated with amoxicillin/clavulanate. Both the ITT and clinical PP follow-up populations were generally well matched for baseline demographics between the two groups, although slightly more males than females received amoxicillin/clavulanate (*Table 1*). While clinical characteristics and smoking history were also generally comparable between the two groups, a greater proportion of gemifloxacin-treated patients had expe-

TABLE 1 - *Patient characteristics at screening (ITT and clinical PP follow-up populations).*

Characteristic	ITT		Clinical PP follow-up	
	Gemifloxacin 320 mg od (n=304)	Amoxicillin/clavulanate 500/125 mg tid (n=296)	Gemifloxacin 320 mg od (n=264)	Amoxicillin/clavulanate 500/125 mg tid (n=266)
Gender, n. (%)				
Male	162 (53.3%)	177 (59.8%)	141 (53.4%)	157 (59.0%)
Female	142 (46.7%)	119 (40.2)	123 (46.6%)	109 (41.0%)
Age (years)				
Mean (SD)	64.2 (11.7)	64.0 (12.1)	64.1 (11.7)	63.8 (12.2)
Range	40-92	41-97	40-92	41-97
Weight (kg)				
Mean (SD)	72.1 (15.5)	74.2 (15.9)	72.5 (15.6)	74.5 (16.3)
Range	38-130	40-148	38-130	40-148
Race, n. (%)				
White	302 (99.3%)	293 (99.0%)	262 (99.2%)	263 (98.9%)
Duration of chronic bronchitis (years)				
Mean (SD)	13.6 (11.6)	13.6 (10.5)	13.5 (11.8)	13.5 (10.6)
Range	1.9-78.8	2.0-58.8	1.9-78.8	2.0-585.8
FEV_1 (% predicted), n. (%)				
<50%	104 (34.2%)	90 (30.4%)	91 (34.5%)	80 (30.1%)
50-70%	70 (23.0%)	80 (27.0%)	60 (22.7%)	73 (27.4%)
>70%	113 (37.2%)	111 (37.5%)	101 (38.3%)	102 (38.3%)
Unknown	17 (5.6%)	15 (5.1%)	12 (4.5%)	11 (4.1%)
Exacerbations treated with antibacterials in previous year, n. (%)				
0	19 (6.3%)	24 (8.1%)	17 (6.4%)	24 (9.0%)
1-4	226 (74.3%)	231 (78.0%)	193 (73.1%)	203 (76.3%)
>4	58 (19.1%)	41 (13.9%)	53 (20.1%)	39 (14.7%)
Unknown	1 (0.3%)	0	1 (0.4%)	0
Smoking history (n. of pack yrs), n. (%)				
0	96 (31.6%)	96 (32.4%)	88 (33.3%)	86 (32.3%)
>0-30	112 (36.8%)	113 (38.2%)	96 (36.4%)	103 (38.6%)
> 30	92 (30.3%)	82 (27.7%)	77 (29.2%)	73 (27.4%)
Unknown	4 (1.3%)	5 (1.7%)	3 (1.1%)	4 (1.5%)
Smoked regularly in past month, n. (%)				
Yes	103 (33.9%)	117 (39.5%)	90 (34.1%)	106 (39.8%)

rienced more than four exacerbations requiring antibacterial therapy in the year prior to study entry (19.1% versus 13.9% on amoxicillin/clavulanate for the ITT population, with similar proportions in the clinical PP follow-up population). Baseline FEV_1 was less than 50% of predicted in approximately one-third of patients in each treatment group. Most study participants were classified as having stage 2 AECB at study entry (90.8% versus 94.6% for the two groups, respectively; ITT population), with a further 8.9% of gemifloxacin-treated patients and 5.4% of those who received amoxicillin/clavulanate having severe, stage 3 disease.

Clinical efficacy

The clinical success rates at follow-up in the clinical PP population were 93.6% for gemifloxacin and 93.2% for amoxicillin/clavulanate. The 95% CI for the treatment difference was -3.9 to 4.6%, demonstrating that gemifloxacin was at least as effective as amoxicillin/clavulanate in terms of clinical response. Clinical success rates were 95.5% and 96.7% in the two groups, respectively, at the end of therapy and 87.2% and 87.4% at long-term follow-up (*Figure 1*). In all, 6.0% of gemifloxacin-treated patients and 5.5% of those who received amoxicillin/clavulanate experienced a clinical recurrence between the follow-up and long-term follow-up visits.

Clinical evaluation revealed a rapid improvement in signs and symptoms of AECB in both treatment groups on therapy. Similarly, there was a marked decrease in the proportions of patients with auscultatory findings on chest examination during the course of the study. The proportions of patients with wheeze decreased from 79.9% in the gemifloxacin group and 76.7% in the group randomized to amoxicillin/clavulanate at screening to 28.8% and 31.2%, respectively, at follow-up, with the proportions of patients with rales decreasing from 75.8% to 17.0% for gemifloxacin and from 82.8% to 18.0% for amoxicillin/clavulanate over the same period of time. Small but sustained improvements in pulmonary function were also apparent during the study. Percent predicted flow rate increased from 51.2% at screening to 56.2% at follow-up with gemifloxacin and from 50.9% to 60.3%, respectively, with amoxicillin/clavulanate.

Bacteriological efficacy

At least one pathogen was isolated at screening in 16.8% of patients in the gemifloxacin treatment group and 16.6% of those randomized to receive amoxicillin/clavulanate (ITT population). *M. catarrhalis* was the most prevalent pathogen, being isolated from 31.4% and 26.5% of patients in the two groups, respectively (bacteriology ITT population) (*Table 2*). *H. influenzae* was more commonly isolated in patients randomized to receive gemifloxacin, while *S. aureus* was more common in

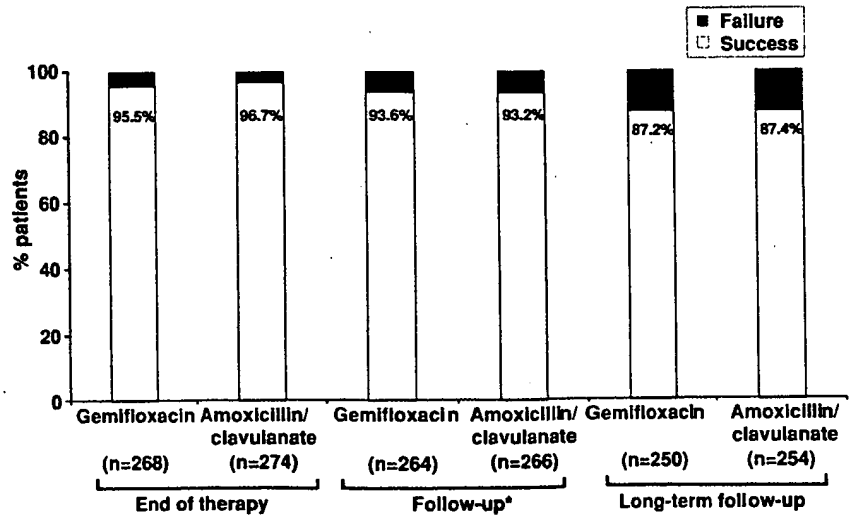

FIGURE 1 - Clinical success rates at the end of therapy, follow-up and long-term follow-up by treatment group (clinical PP population). *Primary efficacy parameter. 95% CI for treatment difference (gemifloxacin - amoxicillin/clavulanate) -3.9 to 4.6.

those assigned to amoxicillin/clavulanate. *Table 3* shows the susceptibilities of these key pathogens to the study drugs compared with those of a panel of other antibacterials, including quinolones, cephalosporins and macrolides. For each key pathogen, the minimum inhibitory concentrations (MICs) for gemifloxacin were generally the lowest of all antibacterials tested.

At screening, 93% of *M. catarrhalis* isolates were found to produce β-lactamase, as were 9.5% of *H. influenzae*, 50% of *H. parainfluenzae* and 91% of *S. aureus* isolates. Some 10.5% of *S. pneumoniae* isolated were found to be resistant to penicillin, with intermediate susceptibility documented in a further 16%. However, with the exception of a single *S. aureus* isolate, which was also resistant to methicillin, the MICs of gemifloxacin against all of these β-lactamase-producing or penicillin-resistant isolates remained low. The *S. aureus* exception had a gemifloxacin MIC of 4.0 μg/ml. Many initial pathogens also showed evidence of resistance to macrolide antibacterials (54% of *S. aureus*, 26% of *S. pneumoniae* and approximately 5% of *H. influenzae*). Again, the gemifloxacin MIC remained low against these macrolide-resistant isolates. Two *S. aureus* isolates were found to be resistant to some quinolone antibiotics; in both cases, gemifloxacin had the lowest MIC of all quinolones tested.

TABLE 2 - *Number of patients (%) with key pathogens associated with AECB at screening (bacteriology ITT population).*

Pathogen	Gemifloxacin 320 mg od (n=51)	Amoxicillin/clavulanate 500/125 mg tid (n=49)
M. catarrhalis	16 (31.4%)	13 (26.5%)
H. influenzae	13 (25.5%)	8 (16.3%)
S. pneumoniae	9 (17.6%)	10 (20.4%)
H. parainfluenzae	2 (3.9%)	0
S. aureus	1 (2.0%)	10 (20.4%)

Bacteriological response rates favored gemifloxacin at all time points (*Figure 2*). For the bacteriology PP population, the bacteriological success rates at follow-up were 90.9% for gemifloxacin and 79.5% for amoxicillin/clavulanate (95% CI -3.3 to 26.0). Similar findings

TABLE 3 - In vitro *susceptibilities (MIC_{90} in mg/ml, unless range is specified) of key pathogens isolated from the bacteriology ITT population to gemifloxacin, amoxicillin/clavulanate and other antibacterial agents.*

Antibacterial agent	*M. catarrhalis* (n=29)	*H. influenzae* (n=21)	*S. pneumoniae* (n=19)	*H. parainfluenzae* (n=2)	*S. aureus* (n=11)
Gemifloxacin	0.06	0.03	0.03	0.004–0.008	1
Amoxicillin/clavulanic acid*	1	0.5	2	0.5–2	8
Levofloxacin	0.25	0.5	1	0.03	4
Trovafloxacin	0.12	0.03	0.25	≤0.015–0.06	1
Ciprofloxacin	0.25	0.5	2	£0.015	16
Ofloxacin	1	1	2	≤0.06–0.12	16
Grepafloxacin	0.25	0.25	0.5	≤0.015–0.03	>16
Ampicillin	16	0.5	2***	0.5–64	>16
Cefuroxime	16	2	4	0.5–1	–
Clarithromycn	16	8	> 16	4–8	>16
Azithromycin	4	2	> 64	0.5–1	>64
Trimethoprim/sulphamethoxazole**	2	8	2	0.12–0.25	0.12
Gentamicin	–	–	–	–	0.25

* Amoxicillin/clavulanic acid was tested at a 2:1 ratio; MICs are expressed in terms of the amoxicillin ratio
** Trimethoprim/sulphamethoxazole was tested at a 1/19 ratio; MICs are expressed in terms of the trimethoprim concentration
*** Penicillin tested for *S. pneumoniae*

were observed at the end of therapy and at long-term follow-up. The majority of initial pathogens were eradicated or presumed eradicated at the end of therapy, follow-up and long-term follow-up visits in both treatment groups (*Figure 3*). Only three initial pathogens eradicated or presumed eradicated at the end of therapy were isolated again at follow-up (one isolate of *H. influenzae* in the gemifloxacin group and isolates of *Proteus mirabilis* and *Pseudomonas aeruginosa* in the amoxicillin/clavulanate group). One further isolate (*M. catarrhalis* from a gemifloxacin-treated patient) was presumed to have recurred at follow-up, on the basis of clinical failure in the absence of an evaluable sputum culture. Three pathogens in the gemifloxacin group and two in the amoxicillin/clavulanate group were presumed to have recurred at long-term follow-up. One patient in the gemifloxacin group was also

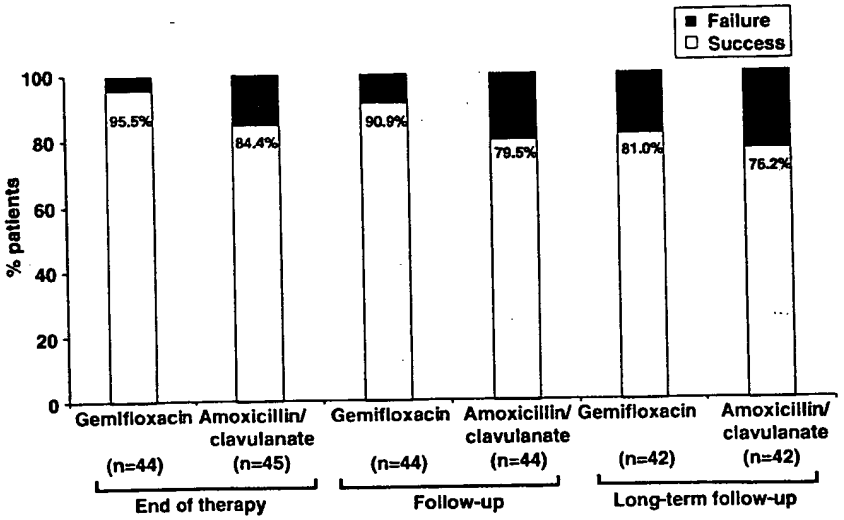

FIGURE 2 - Bacteriological success rates at the end of therapy, follow-up and long-term follow-up by treatment group (bacteriology PP population).

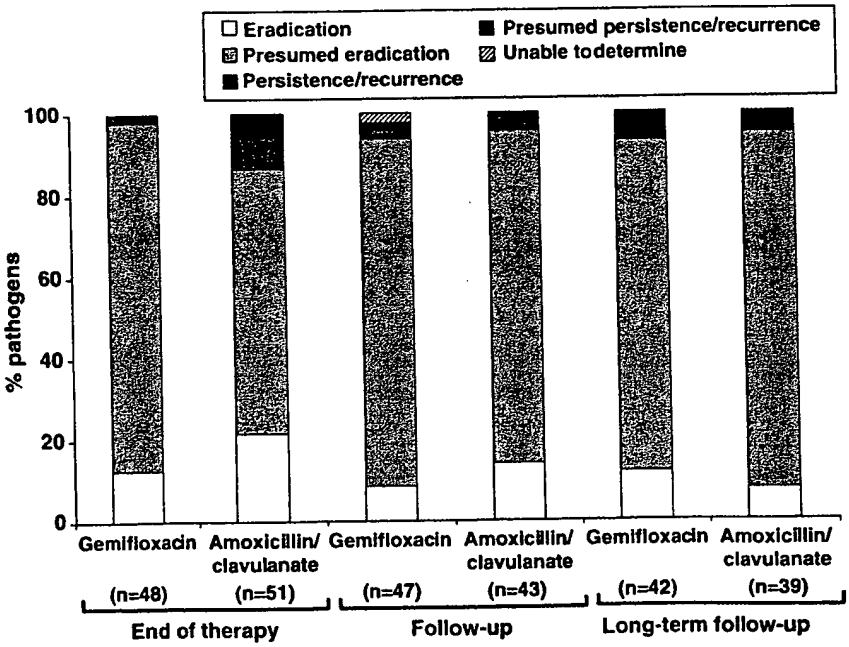

FIGURE 3 - Per-pathogen bacteriological outcome at the end of therapy, follow-up and long-term follow-up by treatment group.

found to have a superinfecting pathogen at the end-of-therapy visit (*P. aeruginosa*), with a new infection documented in another gemifloxacin-treated patient at long-term follow-up (*Enterobacter cloacae*).

Clinical or bacteriological failures could generally not be explained on the basis of MIC values for either of the study drugs, since these were typically low, particularly for gemifloxacin. The highest screening MIC value associated with subsequent treatment failure in the gemifloxacin group was seen in a patient with an initial isolate of *P. aeruginosa* with a MIC for gemifloxacin of 0.5 µg/ml. This patient, who also had an initial isolate of *S. pneumoniae* with a gemifloxacin MIC of 0.03 µg/ml, was a clinical and bacteriological success at the end of therapy, but a failure due to presumed bacteriological recurrence at the follow-up visit. A total of 9 patients treated with amoxicillin/clavulanate had isolates with MIC values ≥1 µg/ml for amoxicillin for either an initial pathogen at screening or persistent/recurrent pathogens or new infections associated with treatment failure (*Table 4*).

Safety

Ninety-five patients (31.3%) who received gemifloxacin and 104 (35.1%) of those treated with amoxicillin/clavulanate reported adverse experiences during the course of this study. Gastrointestinal disturbances were the most common adverse event in both treatment groups, occurring in 10.5% of gemifloxacin-treated patients and 18.9% of those on amoxicillin/clavulanate. The only adverse experience reported by at least 5% of patients in either treatment group was diarrhea, which was significantly more frequent with amoxicillin/clavulanate (11.5% compared with 2.3% for gemifloxacin; $p < 0.01$). Adverse experiences suspected or probably related to therapy were reported in 11.2% of gemifloxacin-treated patients and in 19.3% of patients in the amoxicillin/clavulanate group (*Table 5*).

The proportions of patients withdrawing from the study due to adverse experiences were comparable between the two treatment groups (3.3% for gemifloxacin and 3.0% for amoxicillin/clavulanate). No single adverse experience resulted in the withdrawal of more than one patient in the gemifloxacin group, while 5 patients treated with amoxicillin/clavulanate withdrew due to diarrhea.

TABLE 5 - *Number (%) of patients with adverse experiences suspected or probably related to the study medication (≥1% of patients).*

Adverse experience	Gemifloxacin 320 mg od (n=304)	Amoxicillin/clavulanate 500/125 mg tid (n=296)
Total	34 (11.2%)	57 (19.3%)
Nausea	8 (2.6%)	4 (1.4%)
Diarrhea	7 (2.3%)	31 (10.5%)
Dizziness	3 (1.0%)	3 (1.0%)
Abdominal pain	2 (0.7%)	3 (1.0%)
Vomiting	2 (0.7%)	3 (1.0%)
Dyspepsia	1 (0.3%)	4 (1.4%)

TABLE 4 - *Pathogens associated with clinical or bacteriological failure in either treatment group.*

Pathogen	N. of failures on amoxicillin/clavulanate	Amoxicillin/clavulanate MIC	N. of failures on gemifloxacin	Gemifloxacin MIC
P. aeruginosa	2	16–>32 µg/ml	1*	0.5 µg/ml
P. mirabilis	2	1–4 µg/ml	–	–
S. pneumoniae	1	8 µg/ml	1*	0.03 µg/ml
H. influenzae	1	2 µg/ml	–	–
S. aureus	1	2 µg/ml	–	–
S. marcescens	1	>32 µg/ml	–	–
E. coli	1	8 µg/ml	–	–

* Pathogens isolated from a single patient

The proportions of patients reporting severe adverse experiences were similar in the two treatment groups (3.6% and 4.1%, respectively). The most frequently reported severe adverse events were dyspnea (3 patients) and headache (2 patients) for gemifloxacin, and bronchitis (3 patients) and diarrhea (2 patients) for amoxicillin/clavulanate. Serious adverse experiences occurred in 10 patients (3.3%) treated with gemifloxacin and in 5 (1.7%) of those who received amoxicillin/clavulanate. However, only one of these adverse experiences was suspected or probably related to the study medication (one case of insomnia with gemifloxacin). A total of 3 patients died during the course of the study, all from the gemifloxacin treatment group (2 patients due to respiratory insufficiency and 1 due to cardiac arrest), but none of these deaths were considered related to therapy.

Very few patients experienced vital signs of potential clinical concern during the course of the study (≤1%). The numbers of patients with liver function tests or other laboratory values of potential clinical concern were also low and similar in both treatment groups (<2%).

DISCUSSION

Results from this randomized, well-controlled clinical study clearly demonstrate that gemifloxacin (320 mg once-daily for 5 days) is as effective and well tolerated for the treatment of AECB as amoxicillin/clavulanate (500/125 mg three-times daily for 7 days). High clinical response rates were seen in both treatment groups approximately one week after the end of therapy (93.6% and 93.2%, respectively). The response rates seen in this study are comparable to those of other recently reported trials, some of which included antibacterials dosed more frequently or for longer durations than gemifloxacin (up to 10 or 14 days) [11,15-19,30]. The once-daily dosing regimen and short treatment duration of gemifloxacin does not therefore appear to compromise therapeutic efficacy and may in fact be expected to promote patient compliance with the treatment regimen [31], potentially reducing the risk of development of resistance in the target pathogens.

The most frequent pathogens isolated at screening in this study were *M. catarrhalis, H. influenzae, S. pneumoniae, H. parainfluenzae* and *S. aureus*, all of which are commonly associated with AECB of bacterial origin [4]. The growing incidence of resistance to β-lactam and macrolide antibiotics among these common respiratory pathogens is well documented [5-9]. In this study, almost 55% of baseline isolates showed evidence of b-lactam resistance, with about 15% also resistant to macrolides. In contrast, only two *S. aureus* isolates were found to have reduced susceptibility to quinolone antibiotics at baseline. Despite these underlying levels of antibacterial resistance, bacteriological response rates supported the clinical findings. Overall eradication rates for bacteriologically evaluable patients were also high, particularly in the gemifloxacin group. Most treatment failures could not be explained on the basis of the susceptibility of the initial pathogen, with gemifloxacin MICs generally much lower than those of the other antibacterial agents tested at baseline. The number of patients found to have positive sputum samples in this study was low (17% and 16% of patients in the gemifloxacin and amoxicillin/clavulanate treatment groups, respectively). A possible explanation for this is the transportation of sputum samples to the central laboratory for microbiological assessment. Ideally the sputum samples should have been immediately cultured at the study centers. This may also explain the apparent discrepancy in the rank order of pathogens from the expected of *H. influenzae, S. pneumoniae*, etc.

Recent safety concerns regarding the potential for serious adverse effects with trovafloxacin, one of the newer fluoroquinolones, have highlighted the need for a fluoroquinolone with enhanced Gram-positive activity and a favorable tolerability profile [21,22]. Gemifloxacin was well tolerated in this elderly population with chronic respiratory disease. Withdrawals due to adverse experiences were low in both treatment groups (approximately 3%), with gastrointestinal disturbances the most common adverse event seen in either arm. Only one serious adverse event was reported of suspected or probable relationship to the study drug (one case of insomnia in a gemifloxacin-treated patient). Very few patients had liver function tests or other laboratory values of potential clinical concern during the course of the study.

In summary, the results of this study suggest

that gemifloxacin administered orally once-daily for 5 days is effective and well tolerated as empirical therapy for the treatment of acute bacterial exacerbations of chronic bronchitis, providing a useful alternative to current standards of care.

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